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Latent Class Analysis of Gilles de la Tourette Syndrome using Comorbidities: Clinical and Genetic Implications

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Abstract

Backgound—Susceptibility loci exist for Gilles de la Tourette Syndrome (GTS), but no causative gene has been identified perhaps in part due to phenotypic heterogeneity. This study uses latent class analyses (LCA) to identify GTS subphenotypes, and assesses characteristics and heritability of the classes.

Methods—952 individuals from 222 TS families recruited for genetic studies were assessed. LCA identified a best-fit model for combinations of the diagnoses of GTS, obsessive-compulsive disorder (OCD), OC symptoms and behaviors (OCS/OCB) and attention-deficit hyperactivity disorder (ADHD) in a random sample of one sibling from each family (N=197), a replication sample randomly chosen from the remaining siblings (N=203), and in the entire sample, including all siblings and parents (N=952). Heritabilities were assessed for all categorical diagnoses and the LCA classes using a variance components approach.

Results—In this large sample of TS sib-pairs and their parents, three TS-affected groups were identified, TS + OCS/OCB (class III), TS + OCD (class IV), and TS + OCD + ADHD (class V), in addition to a minimally affected class (I) and a small chronic tics + OCD class (II). There was a preponderance of males and a younger age at onset in more comorbidly affected classes. Only the TS + OCD + ADHD class was highly heritable.

Conclusions—Our data suggest that GTS classes may represent distinct entities, with both shared and unique etiologies. In particular, TS + OCD + ADHD may represent a separate, heritable phenotype that can be used to further inform genetic studies.

INTRODUCTION

Tourette Syndrome (GTS) is a complex neurodevelopmental disorder characterized by the occurrence of multiple motor and vocal tics (1;2). The complexity of GTS is underscored by minor variants, such as chronic tics, comorbid obsessive-compulsive symptoms and behaviors (OCS/OCB), obsessive-compulsive disorder (OCD), and/or attention-deficit hyperactivity

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disorder (ADHD). Hypothesized shared etiologic pathways for GTS, OCD and ADHD have led to their characterization as 'developmental basal ganglia disorders' (3). Although clearly clinically related, the etiological relationships between GTS, OCD, and ADHD are not well defined. Genetic epidemiology studies have suggested that OCD and GTS co-segregate in families, and thus may represent alternate phenotypes of a common gene (4–6). In contrast, although family members of GTS probands consistently show higher rates of ADHD than would be expected by chance, the etiological relationship between GTS and ADHD is not well understood, with extant research suggesting that GTS and ADHD may respond to different genetic substrates (7–10). Segregation analyses further support a complex inheritance for GTS, perhaps reflecting GTS phenotypic and etiologic heterogeneity (11–14).

Despite indications of a clinical and perhaps an etiological relationship between GTS, OCD, and ADHD, joint analyses at the symptom or disorder level have not been conducted. Symptom-level factor analyses could uncover common factors that cut across standard diagnostic categories. Alternately, latent class analyses could uncover classes of individuals with varying combinations of GTS, OCD and/or ADHD. If supported by increased heritabilities, the alternate subphenotypes generated by such studies could be useful in genetic analyses. Such dissection of the phenotype is crucial, given that current data point to multiple genetic susceptibility loci when GTS is viewed as a unitary construct (15–19).

The aims of this study are to: 1) undertake a latent class analysis (LCA) of GTS using categorical diagnoses of OCS/OCB, OCD, and ADHD in a large sample of GTS affected sibpairs and their parents; and 2) characterize the resulting classes in relation to sex, age of onset of tics and class heritabilities. The goal of this study is to determine whether inclusion of OCS/OCB, OCD and ADHD comorbidities in the GTS construct refines the phenotype and can provide support to etiological discovery efforts.

METHODS & MATERIALS

Sample

The sample consisted of 952 individuals from 222 GTS families collected by the Tourette Syndrome Association International Consortium on Genetics (TSAICG) for affected sibling-pair (ASP) genetic linkage studies (18;19). Families were ascertained based on presence of GTS in at least two siblings and the availability of at least one parent. Families were excluded if the proband had mental retardation or a pervasive developmental disorder or where both parents had a known diagnosis of GTS, chronic motor or vocal tic disorder (CT), or OCD. Parents and all siblings known to have a tic disorder at the time of interview were assessed for GTS, chronic tics, OCD, OCS/OCB, and ADHD. Siblings thought to be unaffected were not routinely assessed. The study was approved by the Institutional Review Boards of the respective institutions and written informed consent was obtained. Assent was obtained for subjects younger than 13 years.

Clinical Assessments

Clinical assessments are described in detail elsewhere (18;19). All subjects were directly interviewed using a battery of structured interviews assessing tics, obsessive-compulsive symptoms, and ADHD symptoms using a clinician-reviewed self-report instrument developed by the TSAICG. Children were administered the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) and adults were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (20). Diagnoses of GTS, CT, OCD, and ADHD-inattentive (ADHD-IA), ADHD-hyperactive/impulsive (ADHD-HI), or ADHD-combined (ADHD-C) followed DSM-IV criteria. Present and worst-ever lifetime tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS) (21). A diagnosis of OCS/OCB was made when

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symptoms were present but time criteria were not met (i.e., the subject had at least mild distress and interference, but the symptoms took up less than one hour a day). Final diagnoses for all disorders were assigned by two or more independent clinicians using a best estimate/consensus diagnosis procedure (22).

Statistical Analyses

Demographics—Differences in sex distribution, age at onset of tics and comorbid frequencies of OCD, OCS/OCB, and ADHD subtypes between GTS and CT were assessed using unpaired student t-tests for continuous measures and Pearson chi-square tets for categorical measures.

Latent Class Analysis (LCA)—The diagnostic categories were used in LCA included GTS, OCD and ADHD. Each subject was diagnosed with a) GTS or chronic tics; b) OCD or OCS/OCB; and c) ADHD-combined (ADHD-C), ADHD-hyperactive/impulsive (ADHD-HI), or ADHD-inattentive (ADHD-IA). MPLUS version 3.0 was used for LCA calculations using all diagnoses as categorical variables in the analysis (23). Given the sib-pair composition of the sample and potential non-independence of diagnoses, LCA was first conducted on a random sample of GTS-affected sibs with complete clinical data (n = 197), one from each family, then replicated in a second set of independent GTS-affected sibs randomly chosen from the remaining affected siblings after excluding the first sample (n = 202). Finally, LCA of the whole sample containing all parents and all siblings was completed (n = 952). This strategy allows for a qualitative comparison of LCA of the random subsets of sibs in order to minimize the tendency of sibs to produce non-random classes and sets the context for the omnibus LCA results (n=952).

Fit-Criteria for LCA—The lowest Akaike Information Criteria (AIC), Bayesian information criteria (BIC), and sample size adjusted-Bayesian information criteria (adj-BIC) were used to determine the best-fit model. For competing models, the AIC is defined by the model and the maximum likelihood estimates of the parameters: AIC = $-2 \times \log(\text{maximum likelihood}) + 2 \times$ number of independently adjusted parameters within the model (24). The BIC is similar to AIC except that the dimension of the model, or number of independent parameters, is multiplied by $\frac{1}{2} \times \log(n)$. While AIC uses maximum likelihood, BIC uses the asymptotic behavior of Bayes estimators under a special class of priors to choose the appropriate dimensionality of the model (25). To assess class characteristics, sex and age at onset of tics were compared in LCA classes using a non-parametric test of trend.

Heritability Analysis

Heritability estimates and the corresponding significance levels for the resulting LCA classes were calculated using the Sequential Oligogenic Linkage Analysis Routine (SOLAR) statistical package (26). SOLAR employs a variance components approach using information from all available family members across generations and does not assume an inheritance model. The resultant heritability (h^2) is based on a maximum-likelihood-based variance decomposition approach providing an estimate and a confidence interval. Although developed for quantitative traits, support for discrete traits (i.e., classes) is provided. To maximize the information content, the posterior probability for each individual belonging to each latent class is taken as the quantitative trait in this analysis. Because these posterior probabilities are not independent of one another, and because SOLAR cannot effectively correct for these dependencies, heritabilities for membership in each latent class, which are mutually exclusive, were also calculated. Age at interview and gender were controlled for in these analyses.

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RESULTS

Sample Characteristics

From this sib-pair GTS sample, most affecteds (N=668) had GTS diagnoses (N=596), while a minority had CT diagnoses (N=72). Subjects with GTS had a younger age at onset of tics, and more frequent comorbid OCD and ADHD diagnoses compared to subjects with CT (Table 1).

Considering only GTS subjects, 75% had either OCD or ADHD, with approximately a third of the sample having both OCD and ADHD. The other third had comorbid OCD only, and a smaller subset (10%) had comorbid ADHD only (Figure 1).

Latent class analyses

The first random sib sample consisted of 197 individuals with GTS. The best-fit three-class solution for this sample was represented by: Class I, GTS + OCS/OCB (100%); Class II, GTS + OCD (48%); and Class III, GTS + OCD (71%) + ADHD-Combined (100%). The best-fit three-class solution for the second set of random sibpairs (N = 202) was strikingly similar, and was represented by: Class I, GTS + OCS/OCB (100%); Class II, GTS + OCD (45%); and Class III, GTS + OCD (75%) + ADHD-Combined (100%). Thus, results of the LCA for each of the independent sibling samples were virtually identical, ruling out the concern that non-independence of the subjects significantly modified the class composition. Analyses of the entire sample of 952 subjects comprised of 596 GTS subjects, 72 CT subjects and 284 non-affecteds was then conducted to generate a class solution that would take into account the whole spectrum of tic disorders present in this sample. LCA produced a best-fit five-class solution, which included the three groups described above, as well as a minimal disorder group (class I) and a numerically smaller CT + OCD group (class II). The latent class analysis fit-criteria for all 952 subjects results are presented in Table 2. Fit criteria suggested that the 4-Class or 5-Class solutions were plausible. An inspection of the graphical presentation of the fit-criteria further suggests an overall analytic advantage of the 5-Class solution (Figure 2). Qualitatively, the main difference between the 5-Class and 4-Class solution was the emergence of the relatively small ‘chronic tics’ class in the 5-Class solution. Clinical criteria support a 5-class solution; a ‘chronic tics + OCD’ class, albeit a small proportion of the total, might constitute an alternate phenotype of the genetic susceptibility that is expressed as GTS in other family members. In the 5-Class solution, 30% of the entire sample had minimal symptoms (Class I), 4% were characterized as “chronic tics + OCD” (Class II), 11% were characterized as “GTS only” (class III), 31% were characterized as “GTS + OCD” (class IV) and 23% were characterized as “GTS + OCD + ADHD combined” (class V). The 5-Class solution was thus chosen as the best model (Table 3). Next, tests of trend were undertaken to examine whether sex or age at onset of subjects differentiated between classes, assuming a grading of “severity” from Class I to Class V. A higher proportion of males ($z = -5.88$, $p < 0.001$) and an earlier age at onset for motor tics ($z = -4.11$, $p < 0.001$) and phonic tics ($z = -3.36$, $p = 0.001$) were evident with increasingly comorbid classes (Table 3).

Heritability analyses

To further explore the potential relevance of the class assignments for genetic studies, heritabilities for each of the latent classes were explored using a variance components method (SOLAR). Heritability calculations for the latent class probabilities, where each individual is assigned a probability of belonging to each class, showed that probability classes IV (GTS +OCD) ($p = 0.01$) and V (GTS + OCD + ADHD) ($p = 7 \times 10^{-5}$) were significantly heritable, while classes II (CT + OCD) and III (GTS + OCS/OCB) were not (Table 4). Heritabilities using the categorical variable of class membership showed similar results, with only classes IV and IV having statistically significant heritabilities. These analyses were done in parallel because neither analysis produces a completely reliable heritability estimate: the posterior

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probability analyses have the problem of non-independence of the groups, while the membership analyses have the problem that, while categorical traits are supported by SOLAR, the heritability estimates derived using categorical traits are less accurate. This is clearly shown in the heritability estimate for Class II, which shows a high heritability that is nonetheless not statistically significant because of the large standard error surrounding the estimate. However, both types of analyses gave similar results, suggesting that classes IV and V are consistently heritable. Since the data were ascertained for GTS affected status, Class I (minimal symptoms or unaffected) was not considered for heritability analyses. These results were maintained after controlling for sex and age at interview. With the aforementioned caveats, the heritabilities presented suggest that GTS, OCD, ADHD as a group are familial, and that there are likely to be shared etiological factors in their development, at least in this familial GTS sample.

DISCUSSION

This study represents the first latent class analysis of GTS and its most common comorbidities, OCD and ADHD. We identified three GTS "affected" classes, corresponding to GTS + OCS/OCB (class III; n = 107), GTS + OCD (class IV; n = 300) and GTS + OCD + ADHD (class V; n = 229). Two additional classes were also identified in the larger family sample, minimal disorder (class I; n = 281) and chronic tics (class II; n = 35). We are confident that the LCA classes derived from these analyses are reliable, as the two random sib samples and the omnibus sample replicated the same three affected classes. However, the functional meaning of the classes is somewhat less clear. One potential use of the LCA is to examine the question of whether GTS is predominantly a disorder of motor disinhibition, or should be considered in the larger context of disinhibition across functional realms (e.g., the cognitive disinhibition of OCD and the behavioral disinhibition of ADHD) for genetic and other etiological studies. Etiologically, GTS, OCD and ADHD have common putative abnormalities in the fronto-striatal systems (27–29), and common biological markers have been sought (30;31).

Besides the truly unaffected Class I, a 'minor' version of GTS appears as a separate class once the parents and other sibs are included in the analysis (i.e., Class II: chronic tics + OCD). In addition to chronic tics, 100% of individuals in Class II have OCD, making it plausible that in familial samples the presence of OCD is ubiquitous and may respond to common genes influencing the expression of both tics and OCD.

Class III, characterized by GTS + OCS/OCB, corresponds to the "GTS only" group previously reported in the literature, and is generally considered to be spared of major disability in relation to motor control and executive function (32). Denckla et al. (2006) reported that up to 40% of children with TS are "free of ADHD", noting that they are also free of the motor control and executive control deficits of children with ADHD alone or GTS + ADHD. However, it was also noted that this clinical group had oculomotor control deficits in the initiation of prosaccades, regardless of their ADHD status (33). More recently, Rizzo et al. (2007) confirm that the addition of ADHD to GTS confers greater maladaptive behavior and worse cognitive functioning compared to GTS alone (34). It is important to point out that 100% of members of the "GTS only" class have OCS/OCB. While the relationship of OCS/OCB to OCD remains an area of investigation (35), OCS/OCB associated with GTS have been repeatedly observed to correspond to a specific group of OCD symptoms (36–38), and as discussed below, may represent a different phenomenological entity than OCD rather than a "forme fruste" of OCD.

Class IV is characterized by GTS + OCD and was the most numerous class in our sample, concurrent with other studies (39). GTS + OCD (Class IV) may constitute a more severe form of GTS + OCS/OCB (class III) or be a qualitatively different clinical entity. Coffey et al. (1998) set out to explore the differences between GTS, OCD and GTS + OCD. GTS + OCD was found to have higher rates of bipolar disorder, social phobia, body dysmorphic disorder and ADHD

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than the GTS only and OCD only groups. Since most of the increased comorbidities relate to GTS and not OCD, the authors conclude that GTS + OCD is more related to GTS and qualitatively "more severe" than either of each alone (40). The fact that OCD and OCS/OCB consistently separate into different latent classes in this sample suggests hitherto unidentified but important differences between subclinical and clinical OCD in relation to GTS. Multiple studies note OC phenomenological differences when OCD is comorbid with GTS, such as a younger age at onset of OCD, a male predominance, sensory phenomena, sexual obsessions and hoarding, repeating, and counting compulsions compared to OCD alone (41); these, however, are not the symptoms usually identified in OCS/OCB accompanying GTS (38). The heritability results, which are relatively low but positive for Class IV, and the high frequency of the GTS + OCD class in our sample continue to support a possible common genetic background for GTS and OCD as previously reported (6;7;42)

Class V, GTS + OCD + ADHD, comprises about one-third of GTS individuals in the affected classes and has many "core" GTS characteristics such as a preponderance of males, and an earlier age at onset of motor tics compared to classes III and IV. GTS + OCD + ADHD is also highly heritable in this sample ($h = 0.18 \pm 0.05$; $p = 7 \times 10^{-5}$), with the caveat that the value is not overly high even in complex genetics. These data support the notion that a comorbid syndrome may be heritable in these families. Previous studies provide additional evidence for the hypothesis that GTS, OCD, and ADHD may all be part of a common disinhibition syndrome. Principal component factor analyses in four samples from three studies show that subjects with GTS can be divided into those with a "pure" or simple form consistent with class III (GTS + OCS/OCB), and those with a more complex form, consistent with classes IV (GTS + OCD) and V (GTS + OCD + ADHD) (43–45). In these studies, the "pure" form was essentially comprised of simple tics while more complex forms of tics comprised the additional forms of GTS. In the first study, the "complex" symptoms included such disinhibition syndromes as temper fits, argumentativeness, self-injurious behaviors, copralalia, and imitation, which grouped into one of four identified clusters (termed aggressive disinhibition), that was associated with comorbid ADHD in the sample (43). A related complex compulsive factor comprised of touching, picking, echolalia, and palilalia was also identified in this study, and was also found to be associated with comorbid ADHD, but not OCD. In the second study, which examined two independent samples, the "complex" cluster included symptoms related to disinhibition, reckless and impulsive behaviors, self-injury, injury to others, and coprolalia (44). Membership in the complex cluster was associated with increased tic severity, increased global impairment, need for medication treatment, family history of tics, higher rates of OCD and ADHD, and an earlier age of onset. Finally, a third study also found a "pure tics" factor with two additional more complex factors characterizing some forms of GTS: an "ADHD-aggressive" factor and a "negative affective-OCD" factor (45). A family study of GTS and ADHD has underscored the complex relationship between these two disorders. Relatives of ADHD only probands have more tics than expected, but only when they co-occurs with ADHD; vice versa, relatives of GTS only probands have more ADHD than expected, but only if concurrent with tics. OCD was more common in both groups of relatives compared to control relatives, and the presence of OCD predicted the presence of ADHD and GTS in both groups (10). Future studies that employ symptom-level factor analyses of GTS, OCD, and ADHD in combination may help to further elucidate the relationships between these disorders.

Of interest, there were only 60 subjects or about 10% of GTS subjects who had the combination GTS + ADHD, without OCD, as shown in Figure 1. These subjects did not comprise a large enough group to constitute a separate class analytically. The presence of this subgroup suggests that OCD plays a role mediating the relationship between GTS and ADHD that needs further elucidation (i.e., when GTS and ADHD are comorbid, in most instances OCD is also present).

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In summary, the present study is an attempt to go beyond DSM-IV diagnoses to identify person-centered subgroups of GTS in a refinement of the phenotype for etiological studies, including genetic studies. From a clinical perspective, it will be important to recognize that each of these classes may respond to a different treatment strategies, given possible different underlying biological determinants. From a genetic perspective, our results, while exploratory, suggest that individuals with GTS can be effectively grouped into comorbid subtypes for etiological studies. That is, at least in families with multiple affected individuals, GTS is more likely to occur in the context of OCD and/or ADHD than on its own. While the classes derived from our sample were not in themselves surprising, the heritability estimates were somewhat unexpected. Previous research has suggested that GTS + OCD may represent a heritable subgroup of GTS subjects that may be useful for understanding the genetic contributions to a GTS + OCD syndrome. Concordant with recent reports (46), our results suggest that there may be a more complex subtype, the multiply comorbid, or GTS + OCD +ADHD subtype (class V), that may also be heritable, and may be caused by different or additional susceptibility loci than GTS + OCS/OCB (class III) or GTS + OCD (class IV). Whether these classes represent a continuum of clinical complexity and severity or truly discrete entities is not tested in the current manuscript; future analyses using alternate latent class mixture models or multilevel (severity) latent class models could elucidate this question. By inference, future gene discovery studies may need to consider GTS complex phenotypes in order to more reliably locate susceptibility genes, especially in linkage studies. If this assumption is true, the full expression of the disorder would consist of a multiply affected phenotype, while moderating factors, including environmental factors and partial penetrance of susceptibility genes, may lead to more simple phenotypes

Limitations

The primary limitation of this study relates to the sample composition. Because the sample consists of nuclear families ascertained for having at least two siblings with GTS, there is little phenotypic variability in the offspring generation with regard to tic diagnoses. This decrease in variability for the GTS phenotype may falsely decreaseheritability estimates for class III (GTS + subclinical OCD). Additionally, the relative lack of GTS-unaffected siblings, as well as the lack of additional generations within families, makes segregation analyses and other approaches aimed at identifying transmission patterns impractical. Additional limitations arise with regard to the heritability estimates. Although we are confident that classes IV and V are heritable as a result of our analyses, we are less confident of the precise heritability estimates. Limitations are imposed by the data structure and software, which is unable to correct for the non-independence of class probabilities (i.e., class probabilities have to add up to one). In addition, we do not have data on putative environmental contributors to GTS, OCD, and ADHD, which are ostensibly accounting for variance not explained by the genetic variance (h^2). Despite these limitations, the large sample size and the completeness of the clinical data make it possible to maximize the information available from such a sample in useful and previously unexplored ways. Thus, the current analyses cannot distinguish whether the heritability findings for Class V are due to common genetic factors underlying GTS, OCD, and ADHD, or whether there are other mechanisms at play, such as common environmental factors or assortative mating between individuals with the different disorders.

Finally, the familial nature of the sample, ascertained through having two affected sibs, limits the generalizability of the GTS subtypes and may have implications for gene discovery. For example, the Class V phenotype, a more severe, complex form of the disorder may be caused by a rare high-penetrance genetic variant that is more readily found in multiplex families and would be useful for gene discovery through linkage methods. This same complex phenotype, if responsive to a highly penetrant rare genetic variant, might not be as useful in a large-scale

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genetic association studies that seek to locate more common susceptibility genes of minor effect.

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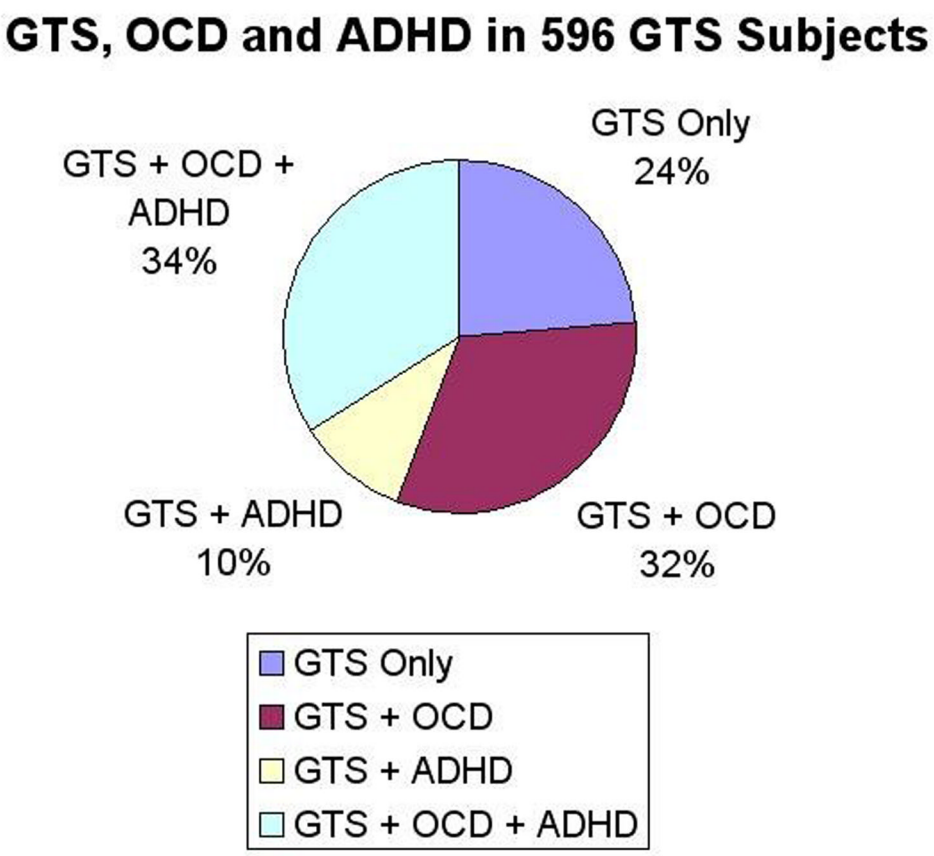

Figure 1.
Comorbidities Associated with Gilles de la Tourette Syndrome in 596 Subjects

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Figure 2.
Fit Criteria for Latent Classes Analysis on 952 Subjects with Gilles de la Tourette Syndrome and their Relatives

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Table 1

Characteristics of Subjects with Gilles de la Tourette Syndrome (GTS) or Chronic Tics (CT) from 222 Tourette Sib-Pair Families.

	Total (N=668)	CT (N= 72)	GTS (N=596)	Significance CT vs. GTS
Sex (% males)	67%	53%	69%	$\chi^2(1) = 7.29$; p = 0.007
Age First Motor Tic	6.34 (3.66)	7.3 (3.6)	6.3 (3.7)	Not Significant
Age First Phonic Tic	7.57 (4.84)	13.3 (11.2)	7.4 (4.4)	4.58 (454); p < 0.0001
Age Worst Motor Tic	10.7 (6.8)	14 (9.3)	10.5 (6.6)	t = 2.516; p = 0.006
Age Worst Vocal Tic	10.8 (7.1)	15.4 (11.7)	10.7 (6.9)	t = 2.360; p = 0.019
OCD	46%	31%	48%	$\chi^2(1) = 7.71$; p = 0.005
Subclinical OCD	18%	18%	18%	Not Significant
ADHD-C	42%	21%	45%	$\chi^2(1) = 14.73$; p = 0.001
ADHD-IA	7%	10%	6%	$\chi^2(1) = 9.65$; p = 0.008
ADHD-HI	4%	6%	4%	Not Significant

OCD = Obsessive-Compulsive Disorder; ADHD = Attention-Deficit Hyperactivity Disorder. C=combined subtype, IA=inattentive subtype, HI=hyperactive/impulsive subtype.

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Table 2

Latent Class Fit-Criteria in 222 GTS Sib-Pair Families and First-Degree Relatives (N = 952) Showing a Best-Fit 5-Class Solution [+]

	1-Class	2-Class	3-Class	4-Class	5-Class	6-Class
Loglikelihood (H_0 Value)	−2865.553	−2673.282	−2566.854	−2534.469	−2508.566	−2503.570
# free parameters	9	15	23	31	39	47
Akaike AIC	5745.107	5376.563	5179.707	5130.938	5095.133	5101.139
Bayesian BIC	5779.139	5449.489	5291.527	5281.651	5284.740	5329.640
Sample Size Adjusted BIC	5756.907	5401.850	5218.480	5183.196	5160.877	5180.370
Pearson Chi-Square	764.755 (df 119)	506.152 (df 111)	224.162 (df 103)	177.285 (df 95)	67.395 (df 88)	56.013 (df 80)
	p-value = 0.0000	p-value = 0.000	p-value = 0.000	p-value = 0.000	p-value = 0.950	p-value = 0.981
Likelihood Ratio	541.856 (df 119)	380.391 (df 111)	169.592 (df 103)	104.677 (df 95)	53.678 (df 88)	43.685 (df 80)
Chi-Square	p-value = 0.000	p-value = 0.000	p-value = 0.000	p-value = 0.233	p-value = 0.999	p-value = 0.997
Entropy		0.746	0.999	0.968	0.922	0.857

[+] Best-Fit Criteria are indicated by: lowest AIC, lowest BIC, lowest sample size-adjusted BIC, less significant chi-square, highest entropy

AIC = Akaike Information Criterion; BIC = Bayesian Information Criteria

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Table 3

Percentage of Individuals in 5 Classes with Gilles de la Tourette Syndrome (GTS), Chronic Tics (CT) Obsessive-Compulsive Disorder (OCD) or Attention-Deficit Hyperactivity Disorder (ADHD) Diagnoses (N=952) [1] in the 5-Class Solution.

Classes	GTS	CT	OCD	S-OCD	ADHD-C	ADHD-HI	ADHD-IA	Total
Minimal Disorder (I)	0%	13%	0%	15%	9%	0%	2%	29.5%
Chronic Tics (II)	0%	100%	53%	17%	29%	9%	15%	3.7%
GTS + S-OCD (III)	100%	0%	0%	100%	36%	6%	4%	11.2%
GTS+OCD (IV)	81%	0%	47%	0%	0%	6%	12%	31.5%
GTS+OCD+ADHD (V)	98%	0%	73%	0%	100%	0%	0%	24.1%
	Class I		**Class II**		**Class III**	**Class IV**	**Class V**	**Total**
Male Sex	50%		34%		67%	60%	76%*	61%
Age Onset Motor Tics	9.1 (7.5)		7.2 (3.5)		6.4 (2.6)	7.0 (5.1)	5.7 (3.1)†	6.7 (4.6)
Age Onset Vocal Tics	11.4 (9.2)		12.3 (8.8)		7.3 (3.2)	7.9 (4.7)	6.9 (4.6)ϕ	7.7 (4.9)
Total	281		35		107	300	229	952

[1] In Class I, for example, no subjects had GTS, 13% had CT, 15% had subclinical OCD, 9% had ADHD combined and 2% had ADHD inattentive, comprising as a whole a minimally affected class. There were a total of 29.5% × 952 = 281 subjects in class I.

S-OCD = Subclinical OCD

ADHD = Attention-Deficit Hyperactivity Disorder (C = combined, HI = Hyperactive-Impulsive, IA = Inattentive)

* Non-parametric test of trend; $z = -5.88$, $p < 0.001$

† Non-parametric test of trend; $z = -4.11$, $p < 0.001$

ϕ Non-parametric test of trend; $z = -3.36$, $p = 0.001$

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Table 4

Intrafamilial Heritabilities for GTS Latent Classes using Posterior Probalities of belonging to a Class for each Individual and Class Membership, Controlling for Sex and Age at interview.

	Heritability (SE)	p-value	Sex	Age At Interview
Probability Class I	NA	NA	NA	NA
Probability Class II	0.10 (0.10)	NS	0.02	NS
Probability Class III	0.0 (0.05)	NS	NS	0.00007
Probability Class IV	0.10 (0.05)	0.01	NS	0.008
Probability Class V	0.18 (0.05)	0.00007	0.05	1.0 × e-15
Membership Class I	NA	NA	NA	NA
Membership Class II	0.49 (0.36)	NS	0.03	NS
Membership Class III	0.0 (0.05)	NS	NS	0.00008
Membership Class IV	0.18 (0.05)	0.02	NS	0.00008
Membership Class V	0.65 (0.14)	0.000002	0.05	6.5 × e-17

Class I = Minimal Symptoms; Class II = Chronic Tics; Class III = GTS + subclinical OCD; Class IV = GTS + OCD; Class V = GTS + OCD + ADHD
NS = not statistically significant; NA = not applicable